REMARKS

Claims 37-80 are pending in the application. Claims 40, 41, 54, 55 and 71-75 have been withdrawn from further consideration as being drawn to non-elected inventions. Claims 37-39, 42-53, 56-70, and 76-80 are under examination. Claims 59 and 76 have been cancelled. Claims 51 and 64 have been amended. Support is found at least in the original claims and in the specification on page 6, lines 1-10. An Appendix of Claims is attached for the Examiner's convenience.

Applicant requests reconsideration of the rejections in view of the following comments with respect to the claims under examination.

Rejections Under 35 U.S.C. § 102(b)

Claims 51-53, 56-59, and 64-66 are rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Saito et al., *Int. Arch. Allergy Immunol.* 107:63-65 (1995). Applicant traverses the rejection.

Anticipation of a claim requires that the reference teach every element of the claim. See MPEP § 2131. Thus, "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." See Vergedaal Bros. v. Union Oil of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Saito describes culturing 5 x 10^7 cord blood mononuclear cells to generate a population of about 5 x 10^7 mast cells. In Saito, cord blood mononuclear cells are grown in media containing SCF (stem cell factor/Steel factor), IL-6, and prostaglandin E_2. As indicated by the initial number of cells used and the number of mast cells generated, there is nominal expansion of the mononuclear cells into mast cells.

Claim 51 recites a population of mast cells comprising at least 10^8 cells. Similarly, Claim 64 recites a substantially pure population of mast cells comprising at least 10^8 cells. The expansion of hematopoietic stem cells into progenitor cells through use of flt-ligand and stem cell factor prior to differentiation into mast cells allows generation of mast cells numbers exceeding those described in Saito. As such, Saito fails to teach all the claim elements and thus

does not anticipate Claim 51 or 64. Claims 52-53, 56-58 and 65-66 ultimately depend from Claim 51 or 64, and therefore are not anticipated by Saito for at least the same reasons.

Claims 51-53, 56-58, and 64-65 are rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Kirshenbaum et al., *Blood* 94:2333-2342 (1999). Applicant traverses the rejection.

Kirshenbaum discloses sorting $CD34^+$ cells into subpopulations and treating the subpopulations in culture medium containing various combinations of cytokines, including SCF + IL-6 + IL-3; SCF + IL-3 + IL-6 + TPO + EPO; and SCF + IL-3 + IL-6 + EPO + GM-CSF. The total number of mast cells described in Kirshenbaum is about 10^6 cells. Kirshenbaum fails to teach a mast cell population comprising at least 10^8 cells. As with Saito, Kirshenbaum does not teach prior expansion of the CD34+ cell population through use of flt-ligand and stem cell factor. Accordingly, Kirshenbaum does not anticipate Claim 51 or 64. Claims 52-53, 56-58 and 65-66 ultimately depend from Claim 51 or 64, and therefore are not anticipated by Kirshenbaum for at least the same reasons.

Rejections Under 35 U.S.C. § 103(a)

Claims 37-39, 42-53 and 56-66 are rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Saito et al., *J. Immunol.* 157:343-50 (1995) in view of Zhang et al., *Chin. J. Biotechnol.* 15:189-94 (1999). Applicant traverses the rejection on grounds that the Patent Office has failed to establish a *prima facie* case of obviousness.

In rejecting claims for obviousness under 35 U.S.C. § 103(a), the Patent Office bears the initial burden of establishing a *prima facie* case of obviousness. See MPEP 2142; see also In re Bell, 26 USPQ2d 1529, 1530 (Fed. Cir. 1993). To establish a *prima facie* case, three basic criteria must be met. First, the prior art must provide one of ordinary skill in the art with a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine their teachings. See WMS Gaming Inc. v. International Game Technology, 51 USPQ2d 1385, 1397 (Fed. Cir. 1999). The mere fact that references could be modified or combined does not render the resulting

modification or combination obvious unless the prior art also suggests the desirability of the modification or combination. See In re Mills, 16 USPQ2d 1430 (Fed. Cir. 1990).

Second, the prior art must provide one of ordinary skill in the art with a reasonable expectation of success. The skilled artisan, in light of the teachings of the prior art, must have a reasonable expectation that the modification or combination suggested by the Examiner would be successful. See In re Dow, 5 USPQ2d 1529 (Fed. Cir. 1988).

Third, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. The teaching or suggestion to the make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, and not in Applicant's disclosure. See In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991). If any one of these criteria is not met, *prima facie* obviousness is not established.

Claim 37 recites contacting CD34 positive cells with a combination of SCF + flt-3 ligand to generate a proliferated population of progenitor cells, and thereafter contacting the proliferated population of progenitor cells with SCF and a cytokine suitable for differentiating the progenitor cells into mast cells.

Saito treats isolated CD34 positive cells or cord blood mononuclear cells (CMBC) with a combination of SCF, IL-6, and prostaglandin E2 to generate a population of mast cells. Saito does not teach or suggest treating CD34 positive cells with SCF + flt-3 ligand to generate a proliferated population of progenitor cells and thereafter treating the proliferated population of progenitor cells with SCF + cytokine to generate a proliferated population of mast cells. The teaching of Saito is a single step procedure for converting CD34+ cells to mast cells. Saito does not teach an initial step for proliferating CD34+ cells into progenitor cells prior to conversion into mast cells.

Zhang discloses *ex vivo* expansion of hematopoietic cells in culture with various cytokine combinations, such as SCF + flt-3 ligand or SCF + flt ligand + IL-3. Zhang, however, provides no teaching or suggestion for contacting the expanded cells with SCF and a cytokine to generate functional mast cells. The reference never distinguishes the cell populations treated with SCF + flt 3 from those treated with SCF+flt-3 + IL-3, other than the ability to form colonies of granulocyte/macrophage (CFU-GM). Conspicuous in Zhang is the conclusion that the best expansion of total cell number occurred with a cytokine combination of flt-3 + SCF + IL-3 + IL-

6 rather than SCF + flt-3. As with Saito, teaching of Zhang is limited to a single step procedure, with no suggestion for an additional step of converting any expanded cell population into mast cells.

At best, the combination of Saito and Zhang would lead the person of ordinary skill in the art to contact a population of CD34 positive cells with a cytokine combination of SCF + flt-3 ligand + IL-3 and/or IL-6 in a single step procedure. Therefore, the references fail to teach or suggest every limitation of Claim 37.

Consequently, the combination of Saito and Zhang is not sufficient to establish a case of *prima facie* obviousness for Claim 37. As all of the other rejected claims depend from or refers to the method of Claim 37, these claims are nonobvious for at least the same reasons. Accordingly, Applicant requests withdrawal of the rejections under 35 U.S.C. § 103(a).

Claims 67-70 and 76-80 are rejected as being allegedly obvious in view of Saito et al., *J. Immunol.* 157:343-50 (1996) and Zhang et al., *Chin. J. Biotechnol.* 15:189-94 (1999), further in view of Demo et al., *Cytometry* 36:340-348 (1999) and Janaki et al., *J. Ethonopharmacol.* 67:45-51 (1999).

Demo teaches use of Annexin V and FACS analysis in studying mast cell degranulation. Janaki teaches inhibition of degranulation by extracts of Algaia roxburghiana and tripterpenes roxburghiadiol A and B. Neither Demo nor Janaki describes using in the screens a proliferated population of mast cells comprising at least about 10^8 cells. Demo and Janaki lack sufficient teaching for the producing the number of mast cell used in the claimed screening method, and therefore fail to cure the deficiencies of Saito and Zhang.

Accordingly, withdrawal of the rejections of Claims 67-70 and 76-80 under 35 U.S.C. § 103(a) is requested.

Rejections Under 35 U.S.C. § 112, second paragraph: indefiniteness

Claims 64-66 are rejected under 35 U.S.C. § 112, second paragraph for being allegedly indefinite in reference to the term "substantially pure". The Examiner contends that the specification does not provide standards for defining the scope of a substantially pure population of cultured mast cells. Applicant traverses the rejection.

Applicant submits that the term is definite when viewed in light of the specification and knowledge in the art. A person of ordinary skill in the art would understand the scope of a substantially pure population of mast cells with a reasonable degree of clarity and particularity to determine whether the claim is infringed. See M.P.E.P § 2193.02.

In particular, the disclosure provides guidelines for measuring whether a population of mast cells made by the method of Claim 37 is substantially pure. Characteristics of the claimed cell populations include the CD (cell differentiation) marker profile as embodied in the cell population FACS profiles in Figure 7 and CD marker content in Figure 9; and the activation characteristics of the cultured human mast cells as provided in Figure 8. The population of mast cells are further distinguished by the presence of mast cell associated proteases tryptase and chymase (see page 11, line 30 to page 12, line 3) and presence of cell surface markers (see page 16, lines 3-30).

Characterization of mast cell populations described above is congruent with the descriptions in the cited references (see, *e.g.*, Saito et al., *J. Immunol.* 157:343-50 (1996), page 348, right column). In view of the content of the disclosure and knowledge in the art, a person of ordinary skill in the art would understand the scope of "substantially pure" for the purposes of determining whether the claims are infringed. See M.P.E.P, *supra*. Accordingly, Applicant requests withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejections Under 35 U.S.C. § 112, first paragraph: enablement

Claims 37-39, 42-53, 56-70 and 76-80 are rejected under 35 U.S.C. § 112, first paragraph for alleged nonenablement. The Examiner appears to focus on the conflicting descriptions in the art of the cellular phenotype of mast cell types made by different methods and the alleged insufficiency in the specification in resolving these variations. Applicant traverses the rejection.

The specification shows that mast cells made by the claimed method display all the characteristics of functioning mast cells. The cell populations express mast cell specific proteases chymase and tryptase, and respond to IgE activation in a manner characteristic of mast cells, including release of biogenic amine histamine; release of granule enzymes tryptase and

hexosaminidase; and generation of cytokines TNF-α, IL-5 and IL-13. The Examiner has not shown any evidence that the cells claimed are not mast cells.

Moreover, the adequacy of enablement does not require the disclosure to resolve discrepancies in the contemporaneous art. The proper test as enunciated by the Federal Circuit is whether experimentation needed to practice the claimed invention is undue or unreasonable. See In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). It is submitted that the standard asserted by the Examiner is neither prescribed in the M.P.E.P or by the courts.

The specification in the present case has clearly met the enablement requirement by disclosing to the person of ordinary skill in the art directions on how to generate the mast cells of the claims without undue experimentation. For example, specific disclosure is given for sources of CD34 positive cells and the factors needed to generate a proliferated population of progenitor cells and differentiated mast cells. To generate mucosal type mast cells (MC_T), the claims and specification recite contacting the proliferated population of progenitor cells with SCF and IL-6. To generate connective tissue type mast cells (MC_{TC}), the claims and specification recite contacting the proliferated population of mast cells with SCF and IL-4. A detailed exemplification of the methods is given in the Examples section of the disclosure.

It is submitted that the specification and working examples enable the full scope of the claims. Accordingly, Applicant requests withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

CONCLUSIONS

Applicant submits that the claims under examination satisfy all of the statutory requirements for patentability and are in condition for allowance. An early notification of the same is kindly solicited. If the Examiner believes that there are further unresolved issues, Applicant encourages the Examiner to contact the undersigned attorney with any questions or concerns by telephone at (650) 494-8700.

No fees are believed due with this response. The Commissioner, however, is authorized to charge any required fees, including fees for extensions of time, or credit any overpayment to

Dorsey & Whitney LLP Deposit Account No. 50-2319 (Docket No. A-70882 (467802-00341)).

Respectfully submitted,

DORSEY & WHITNEY LLP

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By: _____

Euk Y. Oh, Reg. No. 54,345 for
Ann M. Caviani Pease, Reg. No. 42,067

Customer No.: 32940
Dorsey & Whitney LLP
Four Embarcadero Center, Suite 3400
San Francisco, CA 94111
Tel: (650) 494-8700
Fax: (415) 398-3249